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Abstract: IgE-mediated food allergy (FA) has been emerging as a public health priority. It is a potentially life-threatening condition with negative impact on the quality of life of patients and their family and its prevalence is increasing in westernized countries in the recent two decades. The current standard approach to FA consists of the strict avoidance of the triggering food. However, an elimination diet may be difficult and frustrating, above all for those foods (e.g. milk and egg) that are pivotal in the common diet. Oral immunotherapy (OIT) may increase the amount of food that the patient can intake without reaction and reduce the risk of potential life-threatening allergic reactions. It is currently considered the most promising treatment for FA. However, many gaps are still unsolved. Areas covered: The aim of this review is to shed light on the current evidence and the main needs in OIT in order to stimulate the development of longitudinal, prospective, and well-designed studies with the final goal of a 'precision medicine.' Expert commentary: Clinical trials for OIT conducted so far are extremely heterogeneous. The aim in the near future is to identify the most suitable candidates to OIT and algorithms for treatments tailored on well-characterized subpopulations of patients.

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A general strategy for de novo immunotherapy design: the active treatment of food allergy

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Abstract

Introduction: IgE-mediated food allergy (FA) has been emerging as a public health priority. It is a potentially life-threatening condition with negative impact on the quality of life of patients and their family and its prevalence is increasing in westernized countries in the recent two decades.

The current standard approach to FA consists of the strict avoidance of the triggering food. However, an elimination diet may be difficult and frustrating, above all for those foods (e.g. milk and egg) that are pivotal in the common diet.

Oral immunotherapy (OIT) may increase the amount of food that the patient can intake without reaction, and reduce the risk of potential life-threatening allergic reactions. It is currently considered the most promising treatment for FA. However, many gaps are still unsolved.

Areas covered: The aim of this review is to shed light on the current evidence and the main needs in OIT in order to stimulate the development of longitudinal, prospective, well-designed studies with the final goal of a "precision medicine".

Expert Commentary: Clinical trials for OIT conducted so far are extremely heterogeneous. The aim in the near future is to identify the most suitable candidates to OIT and algorithms for treatments tailored on well-characterized subpopulations of patients.

Key words: children, food allergy, mechanism of action, novelty, oral immunotherapy, precision medicine, quality of life, management

1. The previous view for treatment of food allergy

IgE-mediated food allergy (FA) is an emerging public health priority. It is a major cause of life-threatening hypersensitivity reactions [1,2] and its incidence has increased significantly over the past two decades. It is estimated FA affects around 6–8 % of children and 2–3 % of adults in westernized countries. [1,3] Moreover, FA may negatively impact the quality of life (QoL) of patients and their family, since anxiety, fear of accidental exposures, requiring changes in dietary habits and social interactions. [4, 5]

The natural history of the disease is influenced by the food involved. The majority of children with allergy to cow's milk (CM), hen's egg (HE), soy and wheat spontaneously overgrow their allergies over time. [6-11] Conversely, less than 20% of peanut or tree nut allergic patients develop naturally tolerance to these foods. [12, 13] The latter are responsible for the majority of fatal or near-fatal food allergic reactions. [14, 15]

The traditional approach to FA lies on the strict avoidance of the triggering food and keeping as rescue medications (including epinephrine, corticosteroids, and antihistamines) readily available in the event of an allergic reaction occurs. [**16, 17] However, an elimination diet represents often an unrealistic therapeutic option for several reasons. It is difficult and frustrating in patients with persistent FA, above all for those foods (such as CM and HE) that are pivotal in the common diet and, therefore, ubiquitous in store-bought foods, and in home and restaurant recipes. [18] Nothwithstanding, despite efforts to comply with this diet, accidental exposures leading to adverse reactions are frequent. [19] Allergens can be hidden in unsuspecting foods, labeling is often misleading, safe food can be contaminated when served with a dirty utensil and cross-reacting allergens may be present in other alimentary sources. [19]

2. The current view: the active treatment for IgE mediated food allergy

The above mentioned limitations of the food avoidance concurrently with a better understanding in the patho-mechanisms underlying FA have stimulated an increasing interest towards an active treatment of the disease. Since the first case described in 1908 [20], oral immunotherapy (OIT) has gained momentum as a potential curative treatment in patients with persistent FA. [**21] Other routes of administration, including the sublingual (SLIT) and epicutaneous (EPIT) ones are under investigation. However, head to head studies comparing OIT versus SLIT show a better effectiveness of the oral route of administration. [**16, **21] More data about EPIT are currently awaited before it can be recommended. [**16, **21]

OIT implies the reiterated administration of the culprit food. Most protocols consist of three successive phases, respectively: initial escalation, up-dosing, and maintenance. Usually, the initial dose escalation starts with incremental administration of small amounts of food allergen, below the threshold of reactivity, usually over 1–2 days. The up-dosing starts with daily ingestion of the highest dose tolerated during escalation phase; then, doses increased usually weekly or biweekly until the maintenance dose is reached. In the maintenance phase, patients consume the food regularly (often daily) for months or years. However, OIT protocols are widely heterogeneous among studies. There are some rush protocols and slow up-dosing regimens with or without an initial dose escalation day. Unfortunately, the heterogeneity in the populations under study, methods employed and outcomes studied made it challenging to interpret the evidence among studies. [**21]

OIT is a potential curative treatment for FA. It may increase the amount of food that the patient can intake without reaction, and reduce the risk of potential life-threatening allergic reactions. [**21] There is strong evidence for the effectiveness during treatment, also referred as "desensitization" [**21]; this is defined as the ability to safely assume the food-antigen, while consuming the OIT doses regularly. However, a more desirable goal of FA-AIT lies on the effectiveness after discontinuing the treatment, also known as "tolerance" or "post desensitization effectiveness", and referred to the absence of symptoms after ingestion of a normal serving of the culprit food despite a period of absence of exposure and remains still one of the major issues to be clarified. [**21]

2.1 Current gaps

OIT constitues currently the most promising treatment for FA, as able to modulate the specific immune response against the culprit allergen. However, many gaps remain still unsolved (**Table 1**). For istance, OIT is logistically demanding and time-consuming and most patients are affected by side effects though often mild. Furthermore, the patho-mechanisms are overall not well-known yet. There is still a long way to go to determine the extent to which the mechanisms underlying "desensitization" versus "long-term tolerance" are similar or different and to develop tests that can reliably determine the immune status of food allergic subjects. Some of the main gaps are discussed below to stimulate longitudinal, prospective, well-designed studies able to reach the final goal of a "precision medicine" tailored on each single patient suffering from FA.

2.1.1 Standardized products and vehicles

First of all, the availability of standard products results urgent. In order to provide both a reliable diagnosis of clinical allergy (eg. IgE assays, skin prick testing and oral food challenge) and an effective treatment (OIT), the availability of medicinal products plays a pivotal role. To our best knowledge, there are no currently authorized medicinal products in the field of FA. However, some phase 3 clinical trial are ongoing [22] and some preliminary results from the respective Phase 2 studies have been already provided [23] The constallations of products so far used in the different trials are enormously heterogeneous. Typically, the natural-raw form is used [24]. However, the use of different type of processed foods could be an alternative treatment. [25] The presence of the allergens can vary inside a food (e.g. egg white and yolk) but also the duration and type of processing (such as homogenization, dry and most thermal processing, fermentation, hydrolysis, irradiation) and the food matrix may influence the allergenic potential and, therefore, the ability of foods to elicit allergic reactions.[26] For instance, the majority (50–85%) of egg allergic patients are tolerant to baked egg products as an extensive heating diminishes the allergenicity of egg white proteins [27]; the allergenicity of peanut proteins could be reduced by boiling and, on the contrary, increased by roasting. [28] Furthermore, most studies have focused on peanut, milk, or egg. Other foods should be investigated.

2.1.2 Standardized protocols

The landscape of OIT protocols used in OIT studies is widely heterogeneous. First, the study design may be different (open label versus double blinded, placebo-controlled; randomized controlled trials versus controlled clinical trial; multi-site versus single-site; and so on). Inclusion and exclusion criteria for enrollment vary as well. Some studies included only patients with severe FA [30], and others excluded them [31]. Furthermore, there is lack of evidence in adults. Most studies have been conducted in pediatric population [31] and others in mixed population (children plus adults, with prevalence of children) [**21]. As the natural history of allergies differs among the foods [6-11], it should be useful to perform subgroup analyses based on different ranges of age in childhood in order to better understand the best timing/time-window to start OIT for each culprit food. However, most studies pool data from wide age-range and subgroup analyses are not feasible. [**21]

Duration and dosing in each OIT phase differ among the studies: some regimens have a "rush" phase [32], others a slower schedule with smaller increasing doses and/or interval-length in between. [31] The target maintenance dose ranges widely also for the same food. [34-35] This variability should be considered when the results are compared.

There is evidence that low amount of food used as maintenance doses are able to maintain full desensitization. [36, 37] However, among the main needs still unanswered, to establish validated protocols with optimal dose of the culprit food allergen to be used for maintenance, the length of the maintenance period, and the sustainability of the desensitization process remain still of high priority.

2.1.3 Improvement of post-discontinuation treatment effectiveness

The assessment of standardized protocols relates strictly to the requirements to define clinically relevant outcomes of effectiveness. It is yet unclear which duration and frequency of ingestion of the allergic food(s) are required to maintain desensitization and we are lacking criteria with which to evaluate and diagnose permanent tolerance, too. To this regard, it is important to distinguish the term 'oral tolerance' from 'sustained unresponsiveness'. In both, there is lack of reactivity to ad libitum allergen ingestion. The first implies lifelong tolerance, whereas the second refers to an unknown duration of tolerance, usually achieved as a result of a treatment intervention (i.e. immunotherapy) [37]. A few studies evaluated the post-discontinuation treatment effectiveness and furthermore by different approaches as both the duration of maintenance and the abstinence period (2 weeks to few months), sometimes within the same trial. [24, 25, 29, , 38-45] Re-challenge after varying periods of avoidance has shown rates of non-reactivity to a food challenge ranging from 18%-78% and most subjects still maintained a state of desensitization to a threshold level higher than their screening challenge. [24, 25, 29, , 38-45] Validated protocols with optimal dosing and duration of therapy are urgently required in order to assess the acquisition of the ability to safely consume a normal serving of foods containing the trigger allergen despite a period of absence of exposure.

2.1.4 Mechanisms of action of OIT and markers of response

There is still a long way to go to determine the extent to which the mechanisms underlying 'desensitization' vs. 'sustained unresponsiveness' are similar or different and to develop tests that can reliably determine the immune status of subjects suffering from FA. Similarly to the mechanisms of action in allergen specific immunotherapy explored in allergic rhinitis and insect venom allergy, the protection from reactions in the early stages of immunotherapy are due to decreased activation of mast cells and basophils, which has been seen as early as in the first 3-4 months of OIT. [45- 48] In addition, many other cell types might contribute to early immunotherapy responses but this needs further investigations. The induction of peripheral T cell tolerance is a pivotal step induced by immunotherapy, and in different models various changes in antigen specific T cell populations correlated with tolerance, including increased T-regulatory cells, decreased Th2 cells, and increased anergic T cells. [49,50] The proportion of antigen-specific T cell subsets and the change in the dominant subset may skew towards allergy vs. tolerance. [51] OIT can induce changes in immunoglobulin subsets. Patients undergoing peanut OIT for a median of 41 months had serum increased levels of peanut-specific IgG4 with de novo specificities associated with reduced serum levels of peanut-specific IgE. [52] Although increasing evidence supports a role for antigen-specific IgG4 in directly inducing tolerance, IgG4 levels may also correlate with other mechanisms promoting tolerance.

There is still a long way to go to determine the extent to which the mechanisms underlying 'desensitization' vs. 'sustained unresponsiveness' are similar or different and to develop tests that can reliably determine the immune status of food allergic subjects.

2.1.5 Impact on quality of life and cost-effectiveness

Food allergy is associated with a negative impact on the quality of life [4, 5,52] and the total annual economic burden of patients and their families. [4, 5, 53, 54] On the other side, though a promising therapy for FA, OIT can be linked to anxiety. [**21] OIT is time-consuming, logistically demanding, and most patients are affected by side effects, though usually mild. [**21] However, OIT could possibly lead to significant and long-term improvements in patients and their respective caregivers. [**21, 34, 54, 55] This should be furtherly investigated as well as the cost-effectiveness impact of OIT. [**21] In addition, OIT represents the emerging reality that provides both hope and optimism to patients burdened by persistent food allergy.

3. Indications and patients'selection

OIT is potentially indicated for patients with evidence of persistent FA and in whom avoidance measures are ineffective, undesirable or cause severe limitations to their quality of life. In **Figure 1,** the procedural algorithm for the management of IgE mediated food allergy is represented. Before initiating OIT, a proper diagnosis is mandatory. It is based on a recent, clear clinical history of an acute reaction(s) after consumption of the triggering food and evidence of allergic sensitization towards the latter by skin prick tets and/or sIgE. [**16] Whether the diagnosis is unclear, oral food challenge is required; and the baseline reaction threshold may be used to establish the efficacy of OIT in individual patients. [**21]

OIT is logistically- and time- demanding, based on immunological mechanisms and adverse events (including anaphylaxis) may occur during the treatment. Therefore, it is crucial that OIT is performed only in centres with professional training in FA care and expertise, competencies and full resuscitation facilities to safely deliver this treatment and manage any complications. Only patients who, alongside their families, understand the aim of the treatment and its risks, and who are motivated and adherent may be cadidable to OIT.

Concerning the patient's age, several issues should be considered. There is lack of evidence for adults. Most of the studies enrolled pediatric or mixed populations with heterogeneous age and clinical presentations. [**21] Some studies have included infants and pre-school children who have tolerated FA-AIT safely. [29,30] However, young children might be not able to report early symptoms of allergic reactions and in children with FA -particularly to CM, HE, wheat and soy- is highly likely the development of spontaneous tolerance. [7-11,32,56] Keeping in mind these considerations, it might be more appropriate to wait for the natural acquisition of spontaneous tolerance before starting AIT for these allergens. [7-11,32,56] The right time to commence may be around 4-5 years of age, but this should be decided on an individual basis.

4. Contraindications and Safety

The Latin locution "Primum non nocere" (i.e. "first, to do no harm") is still an axiom central in the medical deontology. Contraindications should be careful evaluated before commencing the treatment. [**21] As OIT is a logistically demanding tretmant affected by the risk of adverse event, a poor compliance represents an absolute contraindication. The latter include also the following: uncontrolled or severe asthma; active malignant neoplasia(s); active systemic, autoimmune disorders; active eosinophilic esophagitis (EoE) or other gastrointestinal eosinophilic disorders; and initiation during pregnancy. Safety is a pivotal issue in any treatment [57-59]. Furthermore, in OIT, it is particularly important, as children are typically involved and potential adverse events are mostly immediate onset, food-induced IgE-mediated reactions, which can lead to anaphylaxis. Thus far, no fatality has been reported in literature, but systemic reactions are consistently described as common. Another adverse reaction, whose potential onset should be monitored consists of eosinophilic esophagitis. [60] An up-to-date meta-analysis conducted by the European Academy of Allergy and Immunology (EAACI) estimates that patients in the OIT-active arm have a 9% higher risk of systemic reaction than those in the placebo groups (RR: 1.16, 95% CI 1.03 – 1.30).[**21] Converserly, the rate of adverse events (AEs) during OIT largely varies in published studies but mild AEs are predominant and only a few dropped out for this reason.[**21] Unfortunately, reporting, description and grading of AEs are heterogenous and imprecise, and this makes it difficult to compare the real occurrence and severity of specific type of AEs among studies [57]. This drawback also affects the identification of risk factors and their avoidance. However, some risk factors are well-known. They include exercise, infection, and menses which may increase the risk of reactions [40], especially during the maintenance phase(s) of OIT, when patients continue treatment at home. Notwithstanding, in OIT studies most adverse reactions have been reported in the absence of these risk factors. [**21] Also some biological and clinical markers have been evaluated. Patients with higher serum specific IgE levels (>8.85 kU/L to ovomucoid in HE-OIT, and >50 kU/L to CM in CM-OIT), higher skin tests (>9 mm to milk in CM-OIT), low threshold of reactivity and/or severe reactions in the entry food challenge or upon accidental exposure, and underlying asthma seem to be at high risk for

repeated reactions and early FA-AIT failure.[58] However, the establishment of a common registry of systemic adverse events and further larger observational and controlled trials are awaited for a precise identification of biomarkers and predictors of severe AEs and, therefore, the necessity of safety measures (such as longer and slower up-dosing phase, premedication with H1-antihistamines, chromones, or even omalizumab).

5. Administration regimen and Adherence

Currently OIT is not standardized but instead tailored to individual patient with consideration of many factors such as severity and type of culprit food, patient's and family's justification, age of subject who undergoes the treatment. Thus far, the use of fresh material or native food for OIT is adivisable to achieve both desensitization and post- desenzitazion effectiveness. Oral Immunotherapy and other forms of AIT for the active treatment of food allergy can be performed in specilized medical centers [**16]. Different schedules and up-dosing regimens were used in clinical trials: rush immnotherapy and slow updosing regimen. [61] Altogether, the amount of tolerated dose(s) of foods is marginally affected by the different regimens. [62] The need for daily dosing raises concern regarding patients' adherence over long periods of time, as well as unintentional dosing interruption(s) due to illness, travel or family problems. Nowdays, it is seems that "ad libitum" consumption of known food allergens to maintain post- desensitization effectiveness does not appear to be required in all cases. Therefore, more flexible maintenance regimens are possible at least for children who have been successfully desensitized [63, 64]. These findings are of pivotal importance because twice weekly maintenance dosing wil represent an attractive approach for long- term food OIT contributing to OIT adherence [63,64]. Furtermore, recently have been shown that adherence to OIT was significantly higher in patients consuming 1200 mg of peanuts (76, 96.1%) vs those consuming 3000 mg (24/35, 72.2%), (P = .001). [65]

6. Desensitization and post desensitization effectiveness

OIT involves ingesting gradually increasing doses of allergenic food and represents the most effective route of administration to induce desensitization to foods, including milk, egg, and penut. Whether OIT can induce post- desensitization effectiveness is still controversial. [**16] Currently oral desensitization represents the first step toward a permanent tolerance or post- desensitization effectiveness. As with other kinds of immunotherapy (i.e for environmental allergenes) the duration of desensitization could be pivotal for achieving post- desensitization effectiveness. It is reasonable to think that in developed countries the almost continuous or frequent ingestion of foods -such as CM or HE- usually present in the diet, after the achievement of desensitization is per se easy to do by patients; thererefore, active specific immunotherapy might be permanently successful for some food allergens, even without long periods of withdrawal. In other words, in good clinical practice for foods such as milk and egg, after the achievement of desensitization, the chance of friendly accompainying patient to post- desensitization effectiveness (tolerance) represents a possible therapeutical option. Of note, long enough trials with appropriate controls on post desensitization effectiveness are awaited.

7. Adjunctive therapies to OIT

In order to improve the effectiveness and the safety profile, a few novel therapeutic approaches are being assessed, most of them in pre-clinical or early clinical trials. In particular, omalizumab, the anti-IgE monoclonal antibody, represents currently the most promising adjunctive treatment. By binding the freely circulating human IgE but not mast cell- or basophil-bound IgE, it makes IgE unable to bind to its specific high affinity receptor (FceRI) on mast cells and basophils. Some studies have already shown that pre-treatment with this expensive therapy could make safer OIT, preventing the systemic reactions while achieving the beneficial effects of desensitization. [*59-6166, 67] Furthermore, OIT is an allergen specific

therapy and, therefore, treating multiple allergies may represent a complex, long and expensive treatment. Theoretically, one such combined approach could be the best therapeutic option in patients with allergies to multiple foods and/or having failed a previous treatment with OIT alone [68]. Notwithstanding, further studies are waited to better clarify optimal doses and schedule of this combined treatment.

Among adjuvants for FA-AIT, modified bacterial products are under investigation since bacteria are potent stimulants of Th1 immune responses. [69, 35]

8. Expert commentary & five-year view

IgE-mediated food allergy represents both a promising and an intriguing field of application for allergen immunotherapy, especially in the oral form. However, the procedure is time-consuming and not devoid of side effects, whereas we know that many children with cow's milk allergy and hen's egg allergy develop tolerance spontaneously and they can be easily managed with allergen avoidance.

Currently, the use of fresh material or native foods is advisable to achieve the goal of desensitization. On the other hand a race to develop commercial treatment for food allergy is ongoing particularly for peanut allergy. Standardized vaccines of known potency are awaited. Currently studied therapies have some limitations such as variety of parameters included in the methods and heterogeneity in the protocols, and do not offer reassurance regarding long-term protection following discontinuation of treatment.

Recently, the European Academy Allergy and Clinical Immunology (EAACI) published meta-analyses and guidelines for AIT for IgE-mediated food allergy. [**16, **21] Notwithstanding, gaps in practical management of AIT could be utilized for patients with persistent IgE-mediated food allergy in clinical centers with an extensive experience and in-depth knowledge of procedure(s) of AIT.

The achievement of post desensitization effectiveness represents a desiderable goal of AIT. This is possible at least for children who have been successfully desensitized to CM. [63] In this context the post-desensitization strategy and AIT for adult patients with food allergy are the areas of research that need progress.

Hopefully, within the next few years clinicians will gain a better understanding of the utility of AIT, discover biomarkers predictive of favorable outcomes and carry on with strategies to improve the active treatment of IgE mediated food allergy (e.g. association with biologicals) in order to provide a 'precision treatment' tailored on the specific features of each patient.

Key issues

• Oral immunotherapy represents an active treatment for IgE-mediated food allergy.

• The management of food allergy is related to the natural history of the disease. Most of chidren allergic to cow's milk and hen's egg overgrow their disease spontaneously. Therefore, for these allergens, OIT should be considered for children older than 4-5 years with persistent allergic symptoms.

• Currently, the use of fresh materials or native foods is advisable.

• OIT should be performed in selected medical centers and under strict medical supervision.

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Table 1. Main current gaps in the evidence of FA-AIT

Main gaps in the evidence of FA-AIT
1. Standardized products
2. Validated and shared protocols
3. Definition of clinically relevant outcomes of effectiveness
4. Improvement of post-discontinuation treatment effectiveness
5. Safety profile
6. Adjunctive treatment(s)
7. Mechanisms of action
8. FA-related quality of life
9. Cost-effectiveness
10. Identification of markers of response
11. “Precision medicine”

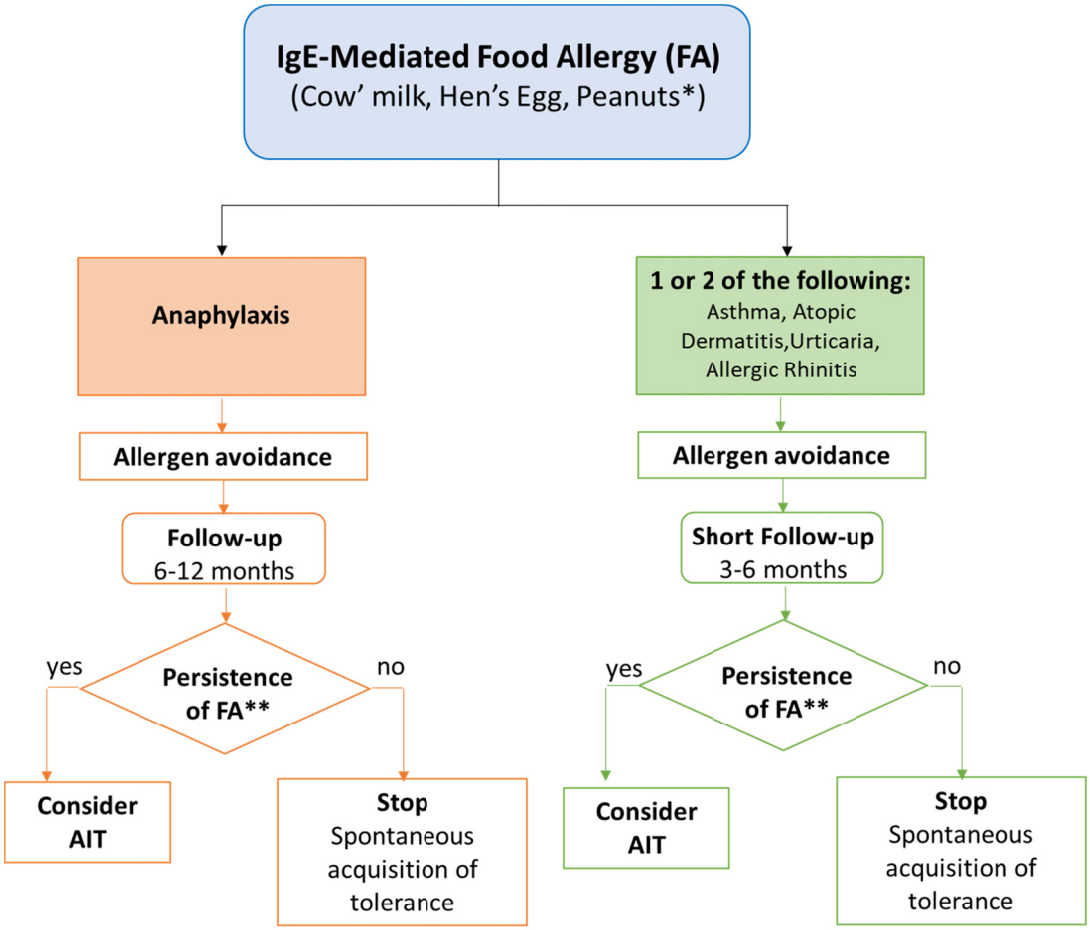

Figure 1: Procedural algorithm for the management of IgE mediated food allergy

*When the patient is a child allergic to cow's milk and/or hen's egg, it is recommended to wait for the natural history of food allergy, i.e spontaneous tolerance (frequently within 4-5 years of age)

**to be assessed by oral food challenge, unless clear history of accidental exposure to the culprit food during the follow-up